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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Paruthi et al. Docket: 1276-4

Serial No.: 10/766,248 Dated: April 9, 2004

Filed: January 27, 2004

For: IMPROVED TASTE MASKING PHARMACEUTICAL COMPOSITION AND PROCESS FOR ITS PREPARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF PRIORITY DOCUMENT

Sir:

Applicants in the above-identified application hereby claim the right of priority in connection with Title 35 U.S.C. §119 and in support thereof, herewith submit a certified copy of Indian Provisional Patent Application Number 131/MUM/2003 filed January 31, 2003.

Respectfully submitted,

Michael E. Carmen
Registration No. 43,533
Attorney for Applicants

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333 Earle Ovington Blvd.
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MEC/bg

CERTIFICATE OF MAILING 37 C.F.R. §1.8(a)

I hereby certify that this correspondence (and any document referred to as being attached or enclosed) is being deposited with the United States Postal Service as first class mail, postage paid in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on April 9, 2004.

Dated: April 9, 2004

Bridget Griffin

INTELLECTUAL PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKSGEOGRAPHICALINDICATIONS

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970.

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 31/01/2003 in respect of Patent Application No.131/MUM/2003 of GLENMARK PHARMACEUTICALS LIMITED, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511, Mumbai – 400 026, India.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

Dated this 13th day of February 2004.

(R. BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1
THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2),7 and Rule 33A)

We, Glenmark Pharmaceuticals Limited, an Indian company having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026 INDIA hereby declare

1.(a) that we are in possession of an invention titled **"AN IMPROVED PALATABLE PHARMACEUTICAL COMPOSITON FOR ORAL ADMINISTRATION AND A PROCESS FOR ITS PREPARATION."**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are **MANOJ KUMAR PARUTHI, SHRIKANT BHONSLE, ANANDI KRISHNAN** All citizens & residents of India belonging to Glenmark Pharmaceuticals Limited , B/2, Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Post Box No.26511 Mumbai – 400 026

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Glenmark Pharmaceuticals Limited
Plot No.A-607, T.T.C Industrial Area
M.I.D.C., Mahape
Navi Mumbai – 400 709
INDIA

ORIGINAL

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
MANOJ KUMAR PARUTHI

(Signed) _____
SHRIKANT BHONSLE

(Signed) _____
ANANDI KRISHNAN

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
(a) Provisional Specification (**08** pages, in triplicate)
(b) Fee Rs. 5000.00 (five thousand rupees only) in bank draft bearing **No. 007973 dated October 21, 2002** drawn on UTI Bank Ltd

We request that a patent may be granted to us for the said invention

Dated this Thirty first (31)st day of January 2003

11 | MUMBAI | 2003
~~133~~ | MUM | 2003
131
31/1/2003

GLENN SALDANHA
Managing Director
Glenmark Pharmaceuticals Limited

भारत सरकार पेटेन्ट कार्यालय शाखा
31 JAN 2003
मुंबई - ४०० ०१३.

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To,
The Controller of Patents
The Patents Office Branch, Mumbai

131 | मुंबई | MUM | 2003
31 JAN 2003

FORM 2

THE PATENTS ACT 1970
(Act 39 of 1970)

PROVISIONAL SPECIFICATION

(SECTION 10)

ORIGINAL

AN IMPROVED PALATABLE PHARMACEUTICAL COMPOSITON FOR ORAL ADMINISTRATION AND A PROCESS FOR ITS PREPARATION

Glenmark Pharmaceuticals Limited, an Indian Company,
registered under the Indian company's Act 1957 and
having its registered office at B/2, Mahalaxmi Chambers, 22, Bhulabhai
Desai Road ,Post Box No. 26511 ,Mumbai - 400 026, India

THE FOLLOWING SPECIFICATION DESCRIBES THE NATURE OF THE INVENTION.

Field of the Invention

The present invention relates to a palatable pharmaceutical composition suitable for oral administration. The invention particularly relates to a pharmaceutical composition effective for taste masking of a pharmaceutical active ingredient when applied as a single layer, over a suitable core containing the said pharmaceutical active ingredient, from an aqueous suspension, using a method, known to the person skilled in the art. The composition of the present invention when s administered orally, is able to provide complete release of the contained active, into the gastric contents within specified period of time thereby ensuring the complete bioavailability of the said active, ingredient . Most preferably the active ingredient is desloratadine but is not limited thereto

wherein, the said coating composition comprises a unique mixture of atleast two water insoluble polymers, out of which at least one is capable of forming a film, along with other suitable pharmaceutical aids and also optionally may contain suitable channeling agents either alone or in combination.

Background of the Invention

Most drugs are preferably formulated as oral dosage forms due to the ease of administration and low cost of development. For patients at the extremes of their age, such as children and the elderly, these formulations are to be provided either as chewable tablets or dispersible tablets or dry powder for reconstitution or as liquid oral dosage forms as they often have difficulty in swallowing the whole tablet. Such formulations allow a greater exposure of the drug to the taste buds resulting in problems of patient compliance when highly bitter or unpleasant tasting drugs have to be administered. In many cases, the objectionable taste cannot be circumvented by use of flavors and sweetening agents.

Current state of the art taste masking technology generally uses microencapsulation techniques which rely primarily on polymer coating materials applied from non-aqueous solutions. The presence of organic solvents may generate regulatory and safety issues and is discouraged in the present scenario due to an increased awareness of health and environmental hazards. Other numerous techniques such as lipid entrapments and complexation with ion exchange resins involve very sophisticated techniques and thus are quite capital intensive.

U. S. Patent No. 5,728,403 (Assignee: *The Board of Regents of the University of Nebraska; Filed: October 5, 1994; Published: March 17, 1998*) describes a pharmaceutical *coating* for taste masking oral medications which includes a unique combination of triglycerides and a polymer. The triglyceride mixture melts at body temperature and the copolymer causes the *coating* to dissolve upon reaching the acidic environment of the stomach. Such a formulation may pose problems during storage and also consistent performance of the composition will be affected due to temperature variations from patient to patient.

U. S. Patent No. 5,075,114 (Assignee: *McNeil-PPC, Inc.; Filed: May 23, 1990; Published: December 24, 1991*) describes a chewable medicament tablets made from coated granules of a medicament wherein the *coating* on said granules comprises a blend of cellulose acetate and/or cellulose acetate butyrate and hydroxy propyl cellulose and a process for making such tablets. Formulations made from the composition described may give some release of the drug when come in contact with liquid in the oral cavity and thus may give bad taste.

U. S. Patent No. 6,451,345 (Assignee: *Eurand Pharmaceuticals Ltd.; Filed: February 17, 2000; Published: September 17, 2002*) describes a taste-masked microcapsules of Linezolid or the like suitable for oral administration as a suspension, a fast-disintegrating, effervescent or chewable tablet, and more specifically relates to such oral dosage forms in which the bitter taste of Linezolid contained therein is masked by a combination of microencapsulation by solvent coacervation and subsequent functional membrane *coating* on said microcapsules.

U. S. Patent No. 5,082,669 (Assignee: *Dainippon Pharmaceutical Co., Ltd.; Filed: July 18, 1990; Published: January 21, 1992*) describes a rapid-releasing oral particle pharmaceutical preparation with its unpleasant taste masked comprising a core and a film layer coating the core, the core at least containing a drug having an unpleasant taste and a water-swelling agent, and the film layer at least containing ethylcellulose and a water-soluble substance. The presence of water soluble substance makes it permeable to liquids and again there is a chance of bad taste appearing in the oral cavity.

None of the approaches reported so far are satisfactory on part of being either very complicated or time consuming and expensive. They are also susceptible to drug leakage either during storage or administration.

There is, therefore, a need to develop an approach for taste masking of bitter and unpalatable pharmaceutical actives, which is stable during storage and does not give any release because of the presence of soluble components in the coating and is inexpensive and easy to use.

Therefore, a primary objective of the present invention is to provide an improved coating for taste masking orally administered pharmaceutical composition drugs and a method for making the same.

Another objective of the present invention is the provide an improved pharmaceutical composition which is non-permeable for taste masking purposes.

Yet another objective of the present invention is the provide an improved pharmaceutical composition for taste masking orally administered drugs which will maintain its integrity during the brief transit period in the mouth but release the medication in the gastric fluid of the stomach.

A still further objective of the present invention is to provide an improved pharmaceutical composition for taste masking orally administered drugs

Yet another objective of the present invention is to provide a method for preparing the improved pharmaceutical composition mentioned above

Detailed Description of the Invention

The present invention comprises pharmaceutical formulations of taste-masked microcapsules which comprise 1) a core of an active ingredient which is most preferably desloratadine, and 2) a polymeric coating that may provide taste-masked characteristics wherein the said coating comprises a mixture of atleast two water insoluble polymers, out of which at least one is capable of forming a film. Both the polymeric coating and the pharmaceutical core may further comprise diluents, fillers and other pharmaceutical additives which may effect the rate of release of active agent(s) from the microcapsule.

Preferably, the polymeric coating composition is comprised of a mixture of atleast two water insoluble polymers, dispersible in water so as to take advantage of aqueous formulation techniques. Aqueous-based coating systems are safe and make regulatory compliance relatively easy compared to non-aqueous based coating systems. A number of polymeric coatings that can provide an elastic microcapsule and will not release active agent in the mouth when administered are contemplated by the present invention.

A preferred coating composition is a mixture comprised of about 25 - 75% of the water insoluble polymer, capable of forming a film and about 30 – 70% of the second polymer, which is present as discrete particles distributed homogeneously throughout the film. More preferably the film forming water insoluble polymer is about 40 – 60% and the second polymer is about 35 – 55% of the total coating composition. The said coating composition may also comprise various pharmaceutical aids.

Examples of water insoluble film forming polymers may include ethylcellulose, for example, Ethocel.TM. brand from Dow Chemical Corp. and other aqueous polymeric dispersions such as Aquacoat.TM. brand from FMC, and Surelease.TM. brand from

Colorcon, polyvinyl acetate, cellulose acetate butyrate, and copolymers of acrylic acid esters, for example, the Eudragit.TM. Copolymers from Rohm Pharma GmbH available as Eudragit L30D-55, Eudragit L100-55, Eudragit RS30D and Eudragit RL30D. Most preferably the water insoluble film forming polymer present is ethylcellulose.

Alternatively, the second water insoluble polymer present as discrete particles may include polymers which are preferably soluble under acidic conditions of the stomach. A preferred polymeric material with such qualities may include polymethacrylic acid ester copolymer available as Eudragit EPO (Rohm Pharma).

An especially preferred embodiment of this invention includes cores of desloratadine as the active agent, coated with a 50:50 mixture of Ethylcellulose and Eudragit EPO, which in turn are formulated as a mouth dissolving tablet. Desloratadine is the anti-allergic drug of choice and is used for treating and/ or preventing allergic and inflammatory conditions of the skin or upper and lower airway pessages, e.g. seasonal allergic rhinitis, perennial allergic rhinitis, or chronic idiopathic urticaria.

A further aspect of this invention is the method for producing the taste-masked microcapsules. In general, the method comprises dispersing coating polymers and other additives in an aqueous vehicle, spraying the coating mixture, drying the coated pharmaceutical core and then pressing the microcapsule into tablets.

In a particularly preferred aspect of the method of this invention ethylcellulose and Eudragit EPO are mixed in a 1:1 weight ratio, and sprayed onto fluidized desloratadine pharmaceutical cores comprised of the drug and various pharmaceutical excipients including fillers, lubricants and binders.

The preferred amount of applied coating is 10 - 30% and more preferably 10 – 20% of the total weight of the microcapsules when the coating is to be applied by the top spray, bottom spray and tangential spray techniques. The preferred uncoated desloratadine core size range is 150 to 500 microns.

Illustrating the invention are the following examples. These examples are for aiding the understanding of the invention, and are not to be construed as limiting the invention to their details.

Example 1

1) PREPARATION OF CORE GRANULES:

Sr.	Ingredient	Qty/Tab. (in mg)
	Granulation	
1	Desloratadine	5.00
2	Lactose anhydrous	13.00
3	Microcrystalline Cellulose	19.50
4	Calcium Carboxymethyl cellulose	3.25
5	Low substituted Hydroxy Propylcellulose	2.20
	Lubrication	
6	Colloidal Silicon dioxide	0.10
7	Magnesium Stearate	0.45

The intragranular materials were blended and granulated after lubrication. The granules obtained were sized to a suitable size range 150 to 500 microns to give core for coating.

2) TASTE MASKING CORE GRANULES BY COATING:

Sr.	Ingredient	Qty/Tab. (in mg)
1	Ethyl cellulose aqueous dispersion	14.5
2	Eudragit EPO	2.75
3	Purified Water	q.s

Eudragit powder was suspended in water and homogenized. The resulting suspension was then added to ethylcellulose aqueous dispersion under stirring, which was then sprayed over fluidized uncoated core particles using Fluidized bed coater with bottom spray attachment (Glatt GPCG1).

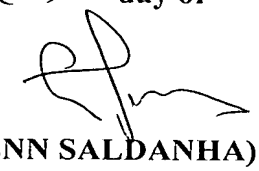
After the optimal weight gain, the coated particles were dried to an optimal moisture level and processed further after mixing with pharmaceutical excipient mannitol to give a desirable tablet dosage form

The coated particles obtained as described in the Example 1 when tasted gave no taste in the oral cavity. The coated particles were then subjected to dissolution as per Pharmacopoeial methods 0 -1N Hcl, Paddle, USP apparatus and it was surprisingly found that maximum amount of drug was released in the first 5 minutes and the complete release took place within 15 minutes.

Advantages of the invention

- Provide an improved coating for taste masking orally administered pharmaceutical composition
- Provides an improved pharmaceutical composition which is non-permeable for taste masking purposes.
- Provides an improved pharmaceutical composition for taste masking orally administered drugs which will maintain its integrity during the brief transit period in the mouth but release the medication in the gastric fluid of the stomach.

Dated this Thirty first (31)st **day of** **January** **2003**



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